

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61L 31/00		A1	(11) International Publication Number: WO 94/21309 (43) International Publication Date: 29 September 1994 (29.09.94)
(21) International Application Number: PCT/BE94/00024 (22) International Filing Date: 24 March 1994 (24.03.94)		(81) Designated States: AU, BG, BR, CA, CN, CZ, HU, JP, NZ, PL, RO, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>	
(30) Priority Data: 9300285 24 March 1993 (24.03.93) BE			
(71) Applicant (<i>for all designated States except US</i>): N.V. D.S.B. [BE/BE]; Meirbrug 1, Bus 2, B-2000 Antwerp (BE).			
(54) Title: POLYURETHANE-COATED INTRAVASCULAR PROSTHESES (STENTS) FOR THE TREATMENT OF BLOOD VESSEL STENOSIS			
(57) Abstract			
<p>A new method to treat blood vessel stenosis using endovascular prostheses which are coated with amphiphilic polyurethanes, to which medicines can be coupled. By coating endovascular prosthesis with amphiphilic polyurethanes, we have succeeded in significantly improving the bio- and bloodcompatibility of endovascular prostheses. These amphiphilic polyurethanes have the property, when implanted in human or animal tissue and blood vessels, of remaining stable and seeming not to provoke an inflammatory reaction. Furthermore it is possible to incorporate medicines in these polymers which, after implantation of the polymers, are slowly released at the location of the place of implantation. This system can further reduce the thrombogenicity of the prostheses coated with the polyurethanes and inhibit the rejection against these prostheses.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

5 POLYURETHANE-COATED INTRAVASCULAR PROTHESES (STENTS) FOR THE
TREATMENT OF BLOOD VESSEL STENOSES. A new method to treat
blood vessel stenoses by means of endovascular protheses
which are coated with amphiphilic polyurethanes to which
medicines can be coupled.

10 DESCRIPTION

Treatment of blood vessel stenoses by means of a balloon catheter is a popular method. Last year, more than
15 6,000 patients with coronary heart disease were treated by this method in our country. The problem with this method is on the one hand the danger that a tear occurs during the blowing up of the balloon whereby the blood vessel can close and thus cause an acute myocardial infarction, on the other hand it is well documented that this treatment method is accompanied by a frequent restenosis of the treated blood vessel within 6 months of the treatment. To solve this problems, medicines were tested in order to prevent the restenosis and furthermore new devices were developed.
20
25 One of these new methods consist of placing a metal intravascular prothesis (stent) at the level of the vessel stenosis. This method is very efficient for treating vessel tears which can occur during balloon dilatation. The problems with this metallic stents however are that they have proven
30 to be thrombogenic and can cause an acute thrombotic occlusion of the treated blood vessel. On the other hand, it appeared that through the inplantation of a metal stent in a blood vessel, the body can react with an inflammatory reaction whereby restenosis within the stent can occur.
35 By covering these endovascular protheses with amphiphilic polyurethanes, we succeeded in significantly limiting both the problem of trombogenecity as well as the problem of reactive hyperproliferative response.
Amphiphilic polyurethanes were synthesized starting from
40 amphiphilic polyester diols on the basis of ethylene oxide and propylene oxide. By reaction with a diisocyanate and a chain lengthener (butanediol), a thermoplastic polyurethane is finally obtained. By the appropriate choice of a) the polyesterdiol, especially the proportion of
45 ethyleneoxide/propyleneoxide, and b) the molecular weight of the diol, the bio- and blood compatibility can be optimized. Furthermore the kind of sterilisation of polyurethane-coated devices turned out to be very critical.
We used certain amounts of gamma radiation which resulted in
50 the formation of further crossbridging of the polymer leading to a more stable and more elastic polymer which is critical during the stent deployment. The resulting polymers turned out to be very stable when implanted in human or animal tissues or blood vessels. Furthermore they did not provoke any inflammatory reaction.
Furthermore we were able to load these polyurethanes with medicines, which were released slowly at the polymer implantation side. These medicines are used to further decrease the thrombogenecity of the stents (heparin, hirudin,
55 streptokinase, urokinase, tpa and other anticoagulants) and
60

5

10 to inhibit the inflammatory reaction caused by the stent (corticosteroids, antimitotics, angiopeptin and other antiinflammatoy drugs.) Using methylprednisolone loaded polyurethane coated stents we were able to block totally the stent restenosis in a pig coronary model.

15

APPLICATION POSSIBILITES OF THE SYSTEM

20

1. Treatment of blood vessel stenosis in humans and animals.
2. Treatment of complications occurring during other treatment methods of blood vessel stenosis.
- 25 3. Treatment of complications occurring during diagnostic procedures.
4. Coating of prosteses, wires, and catheters introduced for
30 medical purposes.

CLAIMS

10

By coating endovascular protheses with amphiphilic polyurethanes, we have developed an efficient method to treat blood vessel stenosis. This method proved to considerably limit the thrombogenicity as well as the rejection against endovascular protheses so that this method signifies an important step forward in the treatment of blood vessel stenosis.

15

INTERNATIONAL SEARCH REPORT

Inten. 1st Application No
PCT/BE 94/00024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 518 704 (SCIMED LIFE SYSTEMS) 16 December 1992 see claims 3,4,9-13 ---	1
Y	WO,A,87 04935 (FISCHEL R.E.) 27 August 1987 see claim 11 ---	1
Y	WO,A,92 15286 (NOVA PHARMACEUTICAL) 17 September 1992 see page 1, line 9 - line 21; claims 1,2,5; example 5 ---	1
P,A	EP,A,0 566 245 (MEDTRONIC) 20 October 1993 see claims 1,3,5,28 --- -/-	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

1 June 1994

08.06.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 cpo nl.
Fax (+ 31-70) 340-3016

Authorized officer

Peltre, C

INTERNATIONAL SEARCH REPORT

Inte: al Application No

PCT/BE 94/00024

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 371 686 (YAMAMOTO N.) 1 February 1983 see column 1, line 6 - line 22 -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/BE 94/00024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 1 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the product."
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/BE 94/00024

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0518704	16-12-92	JP-A-	5200048	10-08-93
WO-A-8704935	27-08-87	DE-A- EP-A, B EP-A- US-A-	3786721 0257091 0556940 4768507	02-09-93 02-03-88 25-08-93 06-09-88
WO-A-9215286	17-09-92	AU-A-	1579092	06-10-92
EP-A-0566245	20-10-93	JP-A-	6007455	18-01-94
US-A-4371686	01-02-83	JP-C- JP-A- JP-B-	1184116 57051718 58008700	27-12-83 26-03-82 17-02-83